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L18: Entry 41 of 78 File: USPT Sep 5, 2000

US-PAT-NO: 6113879
DOCUMENT-IDENTIFIER: US 6113879 A

TITLE: Composition comprising methylphenidate and another drug

DATE-ISSUED: September 5, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Pope; Nicholas Robert	Cambridge			GBX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Medeva Europe Limited				GBX	03

APPL-NO: 9/ 106870 [PALM]
DATE FILED: June 29, 1998

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATION This application is a continuation of application Ser. No. 08/679,878, filed Jul. 15, 1996, now U.S. Pat. No. 5,773,478.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	9514450	July 14, 1995
GB	9608390	April 23, 1996

INT-CL: [7] A61 K 49/00, A61 K 9/16, A01 N 33/02, A01 N 43/06

US-CL-ISSUED: 424/9.1; 424/9.2, 424/490, 435/4, 435/7.4, 435/7.71, 435/7.91, 514/649, 514/922, 514/438
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FIELD-OF-SEARCH: 514/649, 514/438, 514/810, 514/813, 514/922, 424/490, 424/9.1, 424/9.2, 435/4, 435/7.4, 435/7.71, 435/7.91

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5733756	March 1998	Zeitlin et al.	

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ART-UNIT: 165

PRIMARY-EXAMINER: Salimi; Ali

ATTY-AGENT-FIRM: Saliwanchik, Lloyd & Saliwanchik

ABSTRACT:

A method of treating a subject that is undergoing methylphenidate therapy and concomitant therapy with another drug undergoes or interferes with P.sub.450 metabolism, wherein the methylphenidate is d-threo-methylphenidate.

12 Claims, 0 Drawing figures
Exemplary Claim Number: 1

BRIEF SUMMARY:

FIELD OF THE INVENTION

This invention relates to a new composition comprising methylphenidate and another drug, and also to new ways of using known drugs including d-threo-methylphenidate (abbreviated herein as dtmp).

BACKGROUND OF THE INVENTION

Methylphenidate is a known drug (although it is a controlled substance). It is used primarily to treat hyperactive children.

Methylphenidate is a chiral molecule. The properties of the enantiomers have been investigated to some extent, although the drug is still administered as the racemate. It is generally thought that dtmp is the active material, and that its antipode (ltmp) is metabolised more rapidly.

Methylphenidate is often administered in conjunction with other drugs. It is known that the concurrent administration of two drugs that act or are metabolised through

the same metabolic pathway can block that pathway, leading to drug interaction.

Racemic methylphenidate is known to interact clinically with a variety of drugs, such as the tricyclic antidepressants (TCAs), necessitating reduction in the TCA dosage when co-administered to prevent drug interaction (Physicians Desk Reference, Guide to Drug Interactions, 1994).

It is generally believed that the separate enantiomers of chiral therapeutic drugs exhibit different toxicological profiles, with one usually being the main cause of the toxic effects of drug interactions; see Ariens, Schweiz. Med. Wochenschr. 120(5): 131-134 (1990). The basis for this is that each enantiomer will exhibit different preferences for the pathways of enzyme metabolism, e.g. the cytochrome P.sub.450 pathways, and therefore co-administered drugs are blocked at different sites of metabolism.

SUMMARY OF THE INVENTION

It has been discovered that, surprisingly, both dtmp and ltmp similarly inhibit metabolism of other drugs by the cytochrome P.sub.450 systems, in human microsomes. Further, the racemate is shown to have a greater inhibitory profile than either of the enantiomers, suggesting an interaction between the two. Administration of dtmp, substantially free of ltmp, will substantially reduce the inhibition of P.sub.450 isozymes. This has beneficial effects for patients undergoing concurrent administration of other drugs. To avoid the resultant risk of drug--drug toxicity, the present invention involves the administration of that other drug and dtmp. The two drugs used in this invention may be administered sequentially, concurrently or simultaneously, by the same or separate means.

The discovery is based on data showing that, surprisingly, dtmp administration results in less toxicity in the mouse liver than racemic methylphenidate, possibly due to less inhibition of hepatic cytochrome P.sub.450 enzymes. The experiments and data are summarised below. The invention is thus of particular utility in that proportion of the population in which the relevant enzymes have reduced efficiency, or that are receiving the cross-reacting drugs, e.g. SSRIs, in therapy of, say, anxiety or depression.
DETAILED DESCRIPTION:

DESCRIPTION OF THE INVENTION

The dtmp that is used in this invention is substantially free of ltmp, e.g. in an enantiomeric excess (ee) of at least 70%, preferably at least 90%, and more preferably at least 95%. The dtmp may be substantially enantiopure. It may be used in the form of any suitable salt, e.g. the hydrochloride.

As indicated above, the dtmp and other drug may each be administered independently. The invention is not restricted to any particular route of administration, and it will be generally preferred that the respective drugs are administered by their preferred routes. Thus, the dtmp may be administered by the same means as racemic methylphenidate, e.g. in a sustained-release formulation, e.g. a coated tablet. More preferably, the formulation is as described in the copending Patent Application entitled "Sustained-Release Formulation of Methylphenidate", filed on the same date, also assigned to Chiroscience Limited, and claiming priority from British Patent Application No. 9514451.5. The relevant content of that Application is incorporated herein by reference. Advantages of the use of dtmp are also described therein, and may include linear kinetics within the clinically relevant dose range, the reduction of exposure to a controlled substance, reduced side-effects (which include anorexia, insomnia, stomach ache and headache), reduced hepatotoxicity, reduced abuse potential, reduced C.sub.max, a reduced level of active material even when chewed, reduced patient variability, and less variability between fed and fasted subjects.

By controlling the nature of the formulation, it is possible to control dissolution in vitro, and thus match or exceed the US National Formulary (NF) drug release profile for methylphenidate hydrochloride. Further, when administered to a healthy subject, a serum level of dtmp can be attained that is at least 50% of C.sub.max, over a period of at least 8 hours, e.g. 8-16, 8-12 or 8-10 hours. Thus, for example,

a shorter release period may be preferred or a different period before the serum level drops below a different proportion of C.sub.max.

The serum level may be also controlled so that it remains high during the day, after taking a dosage in the morning, and is reduced in the evening, before it can have any undesirable effect on sleeping patterns.

A formulation of the invention may be a unit dosage such as a tablet, capsule or suspension. A sustained-release formulation may be in matrix, coating, reservoir, osmotic, ion-exchange or density exchange form. It may comprise a soluble polymer coating which is dissolved or eroded, after administration. Alternatively, there may be an insoluble coating, e.g. of a polymer, through which the active ingredient permeates, as from a reservoir, diffuses, e.g. through a porous matrix, or undergoes osmotic exchange. A further option for a sustained-release formulation involves density exchange, e.g. in the case where the formulation alters on

administration, e.g. from microparticles to a gel, so that the active ingredient diffuses or permeates out. Ion-based resins may also be used, the active component being released by ionic exchange, and wherein the rate of release can be controlled by using cationic or anionic forms of the drug.

It is preferred to use a formulation in this invention that is resistant to chewing, e.g. micronised particles that are individually coated and which do not immediately release the active component on chewing, or possibly even actively discourage chewing by their consistency. Formulations of the invention that provide improved release characteristics may also be appropriate for the administration of racemic methylphenidate. Further, many effects, benefits etc. described herein apply to formulations providing immediate release. The various effects etc may be due to the use of dtmp and/or the absence of ltmp.

The other drug may be administered in admixture with the methylphenidate. Alternatively, it may be administered in any other formulation, via any suitable route of administration. Conventional dosing parameters may be adopted, i.e. those which are known to or adapted to the practice of those skilled in the art. For example, the daily dosage of dtmp may be 5 to 60 mg, but will be chosen according to the age, weight and health of the subject, and other factors that are routinely considered by the man skilled in the art.

The dtmp may be administered for its primary utility, i.e. treating hyperactive children, as a stimulant in cancer patients treated with narcotic analgesics, or for treating depression (e.g. in AIDS patients), compulsive shopping disorder, narcolepsy or hypersomnia. These subjects typically suffer other complaints requiring medication. The present invention is particularly adapted to the use of such other drugs, e.g. agents that are adapted to treat CNS disorders (e.g. depression); such agents may be tricyclic antidepressants or SSRIs. Thus, the other drug may be one that has the same mode of action, or which has a similar CNS activity. Alternatively or in addition, the other drug that is used in the invention may be any that undergoes the same metabolic degradation as ltmp, e.g. via the P.sub.450 cytochromes, that interferes with ltmp metabolism, or that has its metabolism interfered with by ltmp.

There are many drugs that may interact with methylphenidate. Examples include anti-depressants.

Particular drugs of interest are those whose metabolism is known to occur via the cytochrome P.sub.450 pathways. For example, clomipramine, desipramine, indoramin, imipramine, phenformin and tropisetron undergo aromatic hydroxylation; amiflamine undergoes N-demethylation; amitriptyline and nortriptyline undergo benzylic hydroxylation; codeine, dextromethorphan, dihydrocodeine, hydrocodone, norcodeine and oxycodone undergo O-demethylation; ethylmorphine undergoes O-de-ethylation; flecainide and methoxyamphetamine undergo O-dealkylation; methoxyphenamine undergoes aromatic hydroxylation and N-demethylation; mexiletine and ondansetron undergo hydroxylation; perhexiline undergoes aliphatic hydroxylation; and thioridazine undergoes side-chain sulfoxidation. These are merely example of drugs that use the given pathways. Other specific drugs of interest are cinnarizine, haloperidol,

maprotiline, paroxetine and perphenazine.

Drugs of particular interest that have been seen to interact with methylphenidate include tricyclic anti-depressants (TCAs) such as amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline or trimipramine; monoamine oxidase inhibitors such as phenelzine, selegeline or tranylcypromine; selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine or sertraline; antipsychotics such as haloperidol; anticonvulsants/antiepileptics such as phenytoin, primidone and diphenylhydantoin; anticoagulants such as warfarin; and other drugs for which interactions have been reported such as isocarboxazid, metaraminol, phenylbutazone, phenylephrine, dopamide, norepinephrine, epinephrine, furazalidone, physostigmine and lithium.

It is often the case that a patient, typically a child, diagnosed as having attention-deficit hyperactivity disorder (ADHD; this term is used herein to include also attention-deficit disorder), has concomitant CNS disorders (whether or not diagnosed) which may require no immediate medication but which indicate the likelihood of a future need for, say, a SSRI or TCA. The use of dtmp is indicated, according to this invention, for such a patient.

Adverse effects (including cognitive and mood deterioration) were seen in children treated with a combination of imipramine and methylphenidate. Lithium significantly reduces the level of arousal-activation, euphoria-grandiosity, and the total score of manic-state ratings following methylphenidate challenge.

Further of 20 patients treated with tricyclics combined with methylphenidate, 3 were withdrawn from the trial due to side-effects. These included dizziness, orthostatic blood pressure changes, dry mouth, increased anxiety and hypomania. Baclofen at 10 mg/kg produced a uniform block of both methylphenidate-enhanced activity and stereotypics in rats within 15 to 25 minutes when administered 10 minutes following methylphenidate. Physostigmine and methylphenidate each antagonised the effects of the other in the treatment of manic patients.

Metabolism of Methylphenidate by Cytochrome P.sub.450

Experiments were carried out to investigate the effect of racemic methylphenidate, dtmp and ltmp on the hepatic cytochrome P.sub.450 pathways. The experimental protocol utilised drugs known to be characteristically metabolised by a specific P.sub.450 isotype, and measured the corresponding "enzyme activity" (see results Table, below) in human microsome preparations, by standard methods; see:

Tolbutamide: Knodell et al, J. Pharmacol. Exp. Thes. 241(3):1012-1019 (1987);

Mephenytoin: Yasumori et al, J. Pharmacol. Exp. Thes. 265 (1):89-94 (1993);

Bufaralol: Kronbach et al, Anal. Biochem. 162:24-32 (1987); and

Lauric Acid: Okita et al, Methods in Enzymology 206: 432-441 (1991).

The involvement of the particular P.sub.450 isotype was confirmed using known standard inhibitor compounds (see results Table), using the indicated inhibitor concentrations. Methylphenidate, dtmp, and ltmp were used at 100 .mu.M.

P.sub.450 Isozyme	Standard Enzyme Activity	% inhibition of Enzyme Activity: Standard Inhibitor & Concentration (.mu.m)	Racemic Methyl-phenidate
			Inhibitor

				phenidate	dtmp	ltmp
2C9	Tolbutamide					
	Sulpha-					
		>90	19	25	34	
	hydroxylase					
	phenazole					
	(100)					
2C19	Mephenytoin					
	Tranyl-					
		83	44	31	33	
	hydroxylase					
	cypronine					
	(50)					
2D6	Bufuralol					
	Quinidine					
		>90	65	64	41	
	hydroxylase					
	(10)					
2B	Lauric acid					
	Disulfuram					
		47	<15	<20		
					<20	
	11- (10)					
	hydroxylase					

The results show that dtmp and ltmp have surprisingly similar profiles of inhibitory activity against the enzymes of the hepatic cytochrome P.sub.450 pathway. Further, racemic methylphenidate appears more inhibitory of certain enzymes than either dtmp or ltmp. A reduction in the inhibition of the enzymes of the P.sub.450 pathway may thus lead to a reduction in drug interaction.

CLAIMS:

What is claimed is:

1. A product comprising d-threo-methylphenidate and another drug, wherein said another drug undergoes or interferes with P.sub.450 metabolism, wherein said d-threo-methylphenidate is for the treatment of attention-deficit hyperactivity disorder.

2. The product according to claim 1, wherein said product is for the treatment of attention-deficit hyperactivity disorder in a pre-pubertal child.

3. A product comprising d-threo-methylphenidate and another drug, wherein said another drug undergoes or interferes with P.sub.450 metabolism, wherein said product is formulated for administration to an adult patient.

4. A method of treating a subject that is undergoing methylphenidate therapy and concomitant therapy with another drug, wherein said another drug undergoes P.sub.450 metabolism, or interferes with P.sub.450 metabolism, said method comprising administering an effective amount of d-threo-methylphenidate to said subject.

5. The method according to claim 4, wherein said d-threo-methylphenidate and said another drug is formulated for administration to an adult patient.

6. The method according to claim 4, wherein said another drug is an antidepressant.

7. The method according to claim 4, wherein said another drug is selected from the group consisting of monoamine oxidase inhibitors, antipsychotics anticonvulsants/antiepileptics, and anticoagulants.

8. The method according to claim 4, wherein said another drug is selected from the group consisting of isocarboxazid, metaraminol, phenylbutazone, phenylephrine, dopamide, norepinephrine, epinephrine, furazalidone, physostigmine and lithium.

9. The method according to claim 6, wherein said antidepressant is selected the group consisting of tricyclic antidepressants and selective serotonin reuptake inhibitors.

10. The method according to claim 4, wherein said d-threo-methylphenidate is for treatment of attention-deficit hyperactivity disorder.

11. The method according to claim 10, wherein said d-threo-methylphenidate is for treatment of attention-deficit hyperactivity disorder in a pre-pubertal child.

12. The method according to claim 4, wherein the subject is being treated for attention-deficit hyperactivity disorder.

L2 ANSWER 18 OF 19 MEDLINE
AN 89207694 MEDLINE
DN 89207694
TI The absorption of sustained-release **methylphenidate** formulations compared to an immediate-release formulation.
AU Patrick K S; Straughn A B; Jarvi E J; Breese G R; Meyer M C
CS Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee, Memphis 38163.
SO BIOPHARMACEUTICS AND DRUG DISPOSITION, (1989 Mar-Apr) 10 (2) 165-71. Journal code: A6C. ISSN: 0142-2782.
CY ENGLAND: United Kingdom
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198908

L2 ANSWER 18 OF 19 MEDLINE

AB A crossover study in 18 subjects evaluated the plasma concentration-time profile of two different 20 mg sustained-release (SR) **methylphenidate** (MPH) tablets administered before breakfast, compared to a 10 mg immediate-release (IR) **tablet** administered before breakfast and again 5 h later, before lunch. Plasma MPH concentrations were determined using a sensitive and precise gas chromatography-mass spectrometry method, incorporating a deuterated internal standard. The mean peak MPH concentration was 6.4 ng ml-1 for the IR product versus 4.6 ng ml-1 and 4.8 ng ml-1 for the two SR formulations. Peak concentrations occurred at 3.3 h after dosing with the SR products, compared to 1.5 h after the first dose of the IR product. The extent of absorption for the three products, as determined from areas under the plasma concentration-time curves, were within 5 per cent of each other. There was no significant difference in rate or extent of absorption between the two SR formulations.

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L18: Entry 56 of 78 File: USPT Feb 23, 1999

US-PAT-NO: 5874090
DOCUMENT-IDENTIFIER: US 5874090 A

TITLE: Sustained-release formulation of methylphenidate

DATE-ISSUED: February 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Baker; Helen Frances	Cambridge			GBX
Gilbert; Julian Clive	Cambridge			GBX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Medeva Europe Limited	London			GBX	03

APPL-NO: 8/ 679875 [PALM]
DATE FILED: July 15, 1996

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GB	9514451	July 14, 1995

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US-CL-CURRENT: 424/400; 424/441, 424/468, 424/470, 424/489

FIELD-OF-SEARCH: 424/400, 424/489, 424/468, 424/457

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	2507631	May 1950	Hartmann et al.	260/294
☐	2838519	June 1958	Rometsch	
☐	2957880	October 1960	Rometsch	
☐	4192827	March 1980	Mueller et al.	525/122
☐	5583140	December 1996	Bencherif et al.	514/299

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Patrick, K. S. et al. (1987) "Pharmacology of the Enantiomers of threo-Methylphenidate" The Journal of Pharmacology and Experimental Therapeutics 241(1):152-158.
Eckerman, D.A. et al. (1991) "Enantioselective Behavioral Effects of threo-Methylphenidate in Rats" Pharmacology Biochemistry & Behavior 40:875-880.

ART-UNIT: 152

PRIMARY-EXAMINER: Schofer; Joseph L.

ASSISTANT-EXAMINER: Benston, Jr.; William E.

ATTY-AGENT-FIRM: Saliwanchik, Lloyd & Saliwanchik

ABSTRACT:

The subject invention pertains to a sustained-release formulation of d-threo-methylphenidate (dtmp). The subject invention also pertains to methods for treating disorders using a sustained-release formulation comprising d-threo-methylphenidate.

16 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

BRIEF SUMMARY:

FIELD OF THE INVENTION

This invention relates to a sustained-release formulation of methylphenidate.

BACKGROUND OF THE INVENTION

Methylphenidate is a known drug. It is used primarily to treat hyperactive children. It is a controlled substance.

Methylphenidate is a chiral molecule. The properties of the enantiomers have been investigated to some extent, although the drug is still administered as the racemate. It is generally thought that d-threo-methylphenidate (abbreviated herein as dtmp) is the active material, and that its antipode (ltmp) is metabolised more rapidly.

Methylphenidate is often administered in a sustained-release formulation. For example, a coated tablet comprising racemic methylphenidate is administered, with a view to maintaining a therapeutically-effective level of the drug in circulation. This formulation does not provide satisfactory or reproducible dosing.

Srinivas et al, Pharmaceutical Research 10(1):14 (1993), disclose a further disadvantage of known methylphenidate sustained-release formulations, i.e. that serum levels of the drug are increased by chewing. Many children chew tablets, and are therefore liable to receive an unnecessarily high dose of a controlled substance.

Patrick et al, Biopharmaceutics and Drug Disposition 10:165-171 (1989), describe the absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. It is suggested that the optimum dosage of methylphenidate for children is 0.5-0.7 mg/kg/day.

SUMMARY OF THE INVENTION

The present invention is based on an appreciation of the fact that, although it is possible to provide a model of chiral drug distribution, and measure the concentration of individual enantiomers and their breakdown products in a subject, over time, this is a poor model for understanding the effectiveness of the

enantiomers. Since, after an initial period, the sustained-release formulation should ideally release the active material as evenly as possible, the administration of a racemate, i.e. of two related compounds, takes no account of interaction between the enantiomers. According to this invention, it has surprisingly been found both that there is considerable interaction, and that dtmp provides relatively linear kinetics within the clinically effective dose range in a suitable model, and is therefore suitable for incorporation in a sustained-release formulation. The experiments and data on which this discovery is based are given below.

DRAWING DESCRIPTION:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a comparison of the area under the curve (AUC; ng.h/ml) for d-threo-methylphenidate (dtmp) and racemic methylphenidate at a range of doses.

DETAILED DESCRIPTION:

DESCRIPTION OF THE INVENTION

The dtmp that is used in this invention is substantially free of its antipode (ltmp), e.g. in an enantiomeric excess (ee) of at least 70%, preferably at least 90%, and more preferably at least 95%. The dtmp may be substantially enantiopure. It may be used in the form of any suitable salt, e.g. the hydrochloride.

The dtmp may be administered by the same means as is known for racemic methylphenidate, in a sustained-release formulation, e.g. a coated tablet. It may be administered in any other conventional sustained-release formulation, via any suitable route of administration. Conventional dosing parameters may be adopted, i.e. those which are known to or adapted to the practice of those skilled in the art.

Compositions of the invention may be administered for known purposes, e.g. the treatment of attention-deficient hyperactivity disorder (ADHD; this term is used herein to encompass attention-deficit disorder) in pre-pubertal children and in adults, as a stimulant in cancer patients treated with narcotic analgesics, and also for the treatment of depression (e.g. in AIDS patients), compulsive shopping disorder, narcolepsy and hypersomnia. By contrast to known formulations of methylphenidate, the present invention may have any or all of the following advantages: linear kinetics within the clinically effective dose range, the reduction of exposure to a controlled substance, reduced side-effects (which include anorexia, insomnia, stomach ache and headache), reduced abuse potential, reduced C.sub.max, a reduced level of active material even when chewed, reduced patient variability, reduced interaction with ltmp or other drugs, and less variability between fed and fasted subjects.

By controlling the nature of the formulation, it is possible to control dissolution in vitro, and thus match or exceed the U.S. National Formulary (NF) drug release profile for methylphenidate hydrochloride. Further, when administered to a healthy subject, a serum level of dtmp can be attained that is at least 50% of C.sub.max, over a period of at least 8 hours, e.g. 8-16, 8-12 or 8-10 hours. Thus, for example, a shorter release period may be preferred or a different period before the serum level drops below a different proportion of C.sub.max.

The serum level may be also controlled so that it remains high during the day, after taking a dosage in the morning, and is reduced in the evening, before it can have any undesirable effect on sleeping patterns. Preferably, the serum level is at least 50% C.sub.max after 8 hours and less than 25% C.sub.max after 12 to 16 hours.

A formulation of the invention may be a unit dosage such as a tablet, capsule or suspension. It may be in matrix, coating, reservoir, osmotic, ion-exchange or density exchange form. It may comprise a soluble polymer coating which is dissolved or eroded, after administration. Alternatively, there may be an insoluble coating, e.g. of a polymer, through which the active ingredient permeates, as from a reservoir, diffuses, e.g. through a porous matrix, or undergoes osmotic exchange. A further option for a sustained-release formulation involves density exchange, e.g. in the case where the formulation alters on administration, e.g. from microparticles to a

gel, so that the active ingredient diffuses or permeates out. Ion-based resins may also be used, the active component being released by ionic exchange, and wherein the rate of release can be controlled by using cationic or anionic forms of the drug.

It is preferred to use a formulation in this invention that is resistant to chewing, e.g. micronised particles that are individually coated and which do not immediately release the active component on chewing, or possibly even actively discourage chewing by their consistency. The various effects etc may be due to the use of dtmp and/or the absence of ltmp.

Comparative Pharmacodynamics of d-threo-methylphenidate and Racemate

The study design was based on that described by Aoyama et al, J. Pharmacobio-Dyn. 13:647-652 (1990). Male Wistar rats were dosed with methylphenidate hydrochloride or its d-isomer at nominal dose levels of

racemate: 1.5, 3, 4.5 or 6 mg base/kg body weight

d-isomer: 0.75, 1.5, 2.25 or 3 mg base/kg body weight

Blood samples were taken pre-dose, and 7 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4.5 h, 6 h, 8 h post-dose. The samples were centrifuged to separate the plasma. Plasma samples were assayed for dtmp, by liquid chromatography mass spectrometry.

The results are shown in the accompanying drawing. FIG. 1 gives a comparison of the AUC (area under the curve) for values, obtained from plasma concentration of dtmp, versus time, for dtmp and methylphenidate (at equivalent dtmp quantities) dosed at a range of dtmp concentrations. Both curves show non-linear kinetics, evident as a point of disjunction in each curve. As the doses administered are increased, the quantity absorbed (i.e. AUC) increases in a linear fashion, until the disjunction, when the absorbed quantity is dramatically increased. This disjunction occurs within the clinically-relevant range (16-140 ng.h/ml in humans) for racemate dosing, but, surprisingly, is outside of this range for dtmp dosing.

This means that conventional dosing of the racemate, which involves increasing amounts of the drug, cannot be satisfactorily controlled. The possibility exists that a dosage will be given that is unnecessarily high.

Administration of dtmp has a surprising beneficial effect, in that a relatively linear dtmp AUC level in serum (lower curve) is achieved within the clinically-relevant range. The point of disjunction occurs outside the clinically-relevant range and, therefore, the flux of drug into and out of the circulatory system is more controllable. This makes dtmp suitable for incorporation in a sustained release formulation.

CLAIMS:

We claim:

1. A method for treating a human subject having a disorder capable of treatment with methylphenidate, which comprises administering to said subject a sustained-release formulation comprising an effective amount of d-threo-methylphenidate, wherein said sustained-release formulation is substantially free of l-threo-methylphenidate.

2. The method according to claim 1, wherein at least the initial dosage is less than 15 mg d-threo-methylphenidate per day.

3. The method according to claim 1, wherein the disorder is attention-deficit hyperactivity disorder.

4. The method according to claim 1, wherein the amount of d-threo-methylphenidate administered is less than 1 mg/kg/day.

5. The method according to claim 1, wherein the amount of d-threo-methylphenidate administered is less than 0.5 mg/kg/day.

6. The method according to claim 1, which comprises administering a formulation comprising less than 20 mg d-threo-methylphenidate per unit dosage.

7. The method according to claim 6, which comprises administering a formulation comprising less than 15 mg d-threo-methylphenidate per unit dosage.

8. The method according to claim 1, wherein said sustained-release formulation is selected. from those comprising a soluble, erodible or otherwise modified coating, and those having an insoluble coating through which the d-threo-methylphenidate passes, in use.

9. The method according to claim 1, wherein said sustained-release formulation comprises d-threo-methylphenidate which is micronised.

10. The method according to claim 1, wherein said sustained-release formulation when administered to healthy subjects, provides a serum level of d-threo-methylphenidate of at least 50% C.sub.max, over a period of at least 8 hours.

11. The method according to claim 10, wherein the period is 8 to 12 hours.

12. The method according to claim 10, wherein the serum level is less than 25% C.sub.max after 12 to 16 hours.

13. The method according to claim 1, wherein said sustained-release formulation upon administration to a healthy subject, provides C.sub.max of 2 to 20 ng/ml at a dosage of at least 2 mg.

14. The method according to claim 10, which on administration to a healthy subject, provides C.sub.max of 2 to 20 ng/ml at a dosage of at least 2 mg.

15. The method according to claim 10, wherein C.sub.max is substantially unaffected by chewing.

16. A method for treating a human subject having a disorder capable of treatment with methylphenidate, which comprises administering to said subject a sustained-release formulation comprising an effective amount of d-threo-methylphenidate, wherein said sustained-release formulation is substantially free of 1-threo-methylphenidate, and wherein said effective amount of d-threo-methylphenidate administered to said subject is about 16 to 140 ng.h/ml.